



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : <b>A61K 7/06, 31/625, 31/425 A61K 31/495</b>		A1	(11) International Publication Number: <b>WO 88/0565</b> (43) International Publication Date: <b>11 August 1988 (11.08.8)</b>
<p>(21) International Application Number: <b>PCT/US88/00232</b></p> <p>(22) International Filing Date: <b>27 January 1988 (27.01.88)</b></p> <p>(31) Priority Application Number: <b>008,186</b></p> <p>(32) Priority Date: <b>28 January 1987 (28.01.87)</b></p> <p>(33) Priority Country: <b>US</b></p> <p>(71)(72) Applicant and Inventor: PROCTOR, Peter, H. [US/US]; Twelve Oaks Medical Tower, 4125 Southwest Freeway, Suite 1616, Houston, TX 77027 (US).</p> <p>(74) Agent: LUNDEEN, Daniel, N.; Pravel, Gambrell, Hewitt, Kimball &amp; Krieger, 1177 West Loop South, Suite 1010, Houston, TX 77027 (US).</p>		<p>(81) Designated States: AT, AT (European patent), AU, BI BE (European patent), BG, BJ (OAPI patent), BI CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, FI, FR (European patent), G (OAPI patent), GB, GB (European patent), HU, I (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NC RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).</p> <p>Published <i>With international search report.</i></p>	

(54) Title: TOPICAL COMPOSITION FOR STIMULATING HAIR GROWTH WITH STABLE FREE RADICALS

(57) Abstract

Topical composition and method for stimulating hair growth. The composition contains, in an occlusive or semiocclusive pharmaceutical carrier, a stable free radical forming substance such as minoxidil, diphenyl hydantoin, diazoxide porphyrin, proxyl, doxyl or tempo, an antiandrogen such as spironolactone, and optimally, a free radical scavenger such as dimethyl sulfoxide, a tertiary phosphine oxide or a retinoid. The method involves applying the composition to skin preferably water-soaked skin, once or twice a day.

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-1-

TOPICAL COMPOSITION FOR  
STIMULATING HAIR GROWTH WITH  
STABLE FREE RADICALS

SPECIFICATION

Field of the Invention

This invention relates to a composition and method for treating baldness, particularly androgenic alopecia.

Background of the Invention

5 Various treatments were available for conditions such as male and female pattern baldness and alopecia areata. Several substances were known to be effective when administered internally, but had undesirable concomitant systemic effects and the hypertrichosis was not confined  
10 to the scalp area. In an effort to avoid these side effects and to confine the hypertrichosis to the scalp area, several attempts were made to apply such substances in a topical preparation to the affected area. However, such attempts had generally been only marginally  
15 successful, and the results obtained with the topical preparation containing the orally effective substances

were comparable to and generally little better than those obtained with topical application of the carrier only.

U.S. Patent 2,986,573 described a process for treating hypertension by administering a 1,2,4-benzothiadiazine 1,1-dioxide, otherwise unsubstituted in the heterocyclic portion of the nucleus, having a saturated lower aliphatic hydrocarbon radical in the 3-position and a chlorine atom or its equivalent on the benzenoid portion of the nucleus in the 6- or 7- position.

U.S. Patent 4,184,039 described the development of uncontrolled hair growth in patients treated orally with 1,2,4-benzothiadiazine 1,1-dioxides; and also described topical application of 6-chloro-3-dimethylaminoethoxymethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide and 6-chloro-3-cyclohexenyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide in DMSO and in suspension to promote hair growth.

U.S. Patents 4,139,619 and 4,596,812 described a process for stimulating the growth of mammalian hair by the application of 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-2-iminopyrimidines to mammalian skin in association with a topical pharmaceutical carrier.

U.S. Patent 4,347,245 described a composition containing spironolactone in a liquid carrier such as alcohol, urea, mineral oil or white petrolatum.

Stewart, M.E. et al., "Antiandrogens and the Skin," International Journal of Dermatology, Vol. 17, pp. 167-179 (1978) described the application to the foreheads of acne patients of 10% cyproterone in 50% aqueous dimethyl sulfoxide, with no reduction in sebum secretion or improvement in acne being produced.

U.S. Patent 4,367,227 described a composition for reducing sebum secretion when applied to the skin, which composition contained cyproterone acetate dissolved in a C<sub>2</sub>-C<sub>3</sub> aliphatic alcohol.

-3-

Summary of the Invention

The present invention provides a topical composition for stimulating the growth of hair including, in a pharmaceutical carrier, (i) a hair growth stimulant, (ii) 5 an antiandrogen, and optimally (iii) a free radical scavenger.

In another aspect, the invention is a method of stimulating the growth of hair by applying to the skin to be treated a composition including, in a pharmaceutical 10 carrier, (i) a hair growth stimulant, (ii) an antiandrogen, and optimally (iii) a free radical scavenger.

Detailed Description of the Invention

Briefly, the composition of the invention includes a 15 pharmaceutical carrier, a hair growth stimulant described in more detail hereinbelow, an antiandrogen and optimally, a free radical scavenger.

The carrier of the composition, in which the hair 20 growth stimulant, antiandrogen and any scavenger will generally be substantially homogenously dispersed, is preferably an occlusive or semi-occlusive preparation which may be a water-in-oil emulsion, but is most preferably an oil-in-water emulsion. As used herein, the terms "occlusive" or "semi-occlusive" are used in 25 reference to a carrier which substantially prevents or inhibits, respectively, evaporation of water from the skin to which it is applied. As examples of non-occlusive carriers, there may be mentioned water, urea, alcohols and glycols such as methanol, ethanol, propanol, butanol, 30 ethylene glycol and propylene glycol, and the like.

Suitable water-in-oil emulsions are commercially available under the designations Aquaphor, cold cream, Eucerin, hydrous lanolin, Hydrosorb, hydrophilic petrolatum, Nivea, Polysorb, Qualatum and Velvachol. 35 Suitable oil-in-water emulsions are available commercially under the designations acid mantle cream, Almay emulsion

cream, Cetaphil, Dermabase, Dermovan, hydrophilic ointment, Keri cream, Lubriderm cream, Multibase cream, Neobase cream, Univase cream, Vanibase cream, and Wibi.

The carrier may further contain various other emollients, emulsifiers, water, perfumes, colorants, preservatives and the like. In a preferred embodiment, the carrier comprises the Dermovan emulsion, propylene glycol and water.

A hair growth stimulant is broadly defined herein as any substance other than the carrier, the antiandrogen and the free radical scavenger which is effective in the present topical composition to promote the growth of hair, especially for treating conditions such as male pattern baldness. In general, pharmacologically acceptable substances which form stable free radicals are contemplated as being suitable hair growth stimulants. The formation of stable free radicals in a substance is attributable to electron acceptance or donation from other radicals or reducing and/or oxidizing species, and is generally confirmed by electron spin resonance spectrometry. Several of such substances, such as minoxidil, diphenyl hydantoin, and diazoxide, are known to promote hair growth when administered internally.

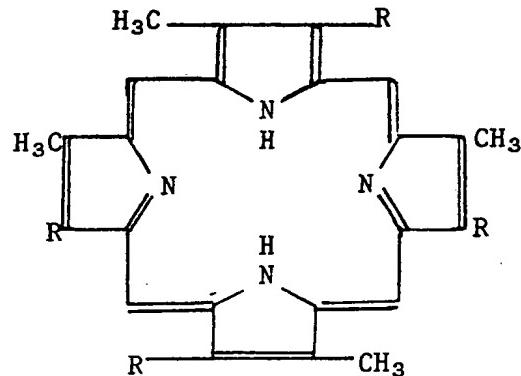
Hair growth stimulants contemplated as suitable in the present composition include minoxidil and the compounds related thereto described in U.S. Patent 3,461,461; 3,382,247 and 3,644,364 which are hereby incorporated herein by reference. Also contemplated as suitable hair growth stimulants are the porphyrins; 5,5-di-substituted- hydantoins; substituted 1,2,4-benzothiadiazine 1,1-dioxides; nitroxide spin labels and spin traps such as doxyl, proxyl and tempo nitroxides; and various nitrones and nitroso spin labels and spin traps described in more detail hereinbelow.

35 Porphyrins are physiologically active nitrogenous compounds, many of which occur naturally. Porphyrins are

-5-

also known as substituted porphines and are derived from the following structure:

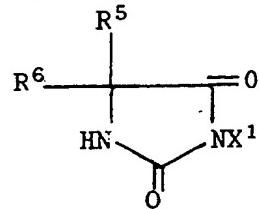
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Specific representative examples of contemplated porphyrins include uroporphyrin, coproporphyrin, 15 protoporphyrin and the like.

Hydantoins contemplated as suitable have the general formula:

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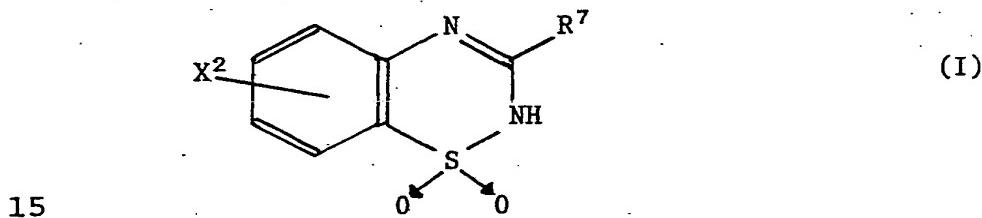
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wherein R<sup>5</sup> and R<sup>6</sup> are independently alkyl, aryl, alkaryl, haloaryl, alkoxyaryl, heteroaryl, aminoaryl or the like, or together are diarylene, and X<sup>1</sup> is hydrogen, alkali metal, alkaline earth metal, ammonium, alkylamine, alkanolamine, polymethylene diamine or the like. Specific representative examples include 5,5-diphenylhydantoin, 5-phenyl-5-(p-bromophenyl)-hydantoin, 5-phenyl-5-(p-chlorophenyl)-hydantoin, 5,5-di-(p-dimethylaminophenyl)-hydantoin, 5-diphenylene-hydantoin, 5-xlenyl-5-phenylhydantoin, 5,5-(di-p-tolyl)-hydantoin, 5-phenyl-5-

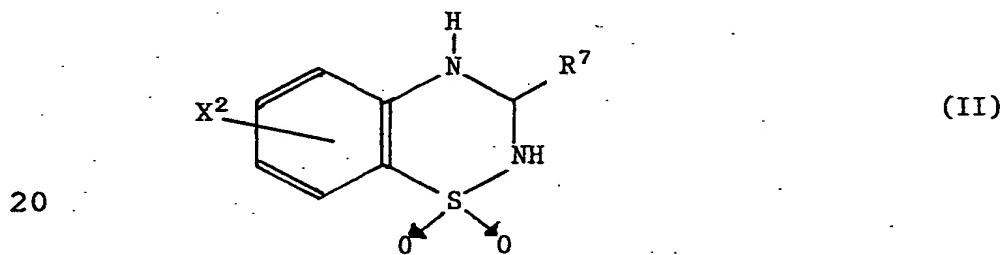
-6-

anisylhydantoin, 5-phenyl-5-(2-thienyl)-hydantoin, sodium salts thereof and the like. Such compounds and their preparation are described, for example, in U.S. Patents 2,366,221 and 2,409,754, which are incorporated herein by reference.

Diazoxide is 7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide. Also contemplated as suitable hair growth stimulants in the composition are the substituted 1,2,4-benzothiadiazine 1,1-dioxides of the general formulae:



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wherein X² is chlorine, bromine or trifluoromethyl in the 6, 7, 8 or 9 position or lower alkyl or lower alkoxy in the 6 position, and R⁷ is alkyl, dialkylaminoalkoxyalkyl, or aralkyl, or a pharmacologically acceptable acid addition salt thereof.

Specific representative examples of contemplated 1,2,4-benzothiadiazine 1,1-dioxides include:  
 3-methyl-7-chloro-2H-1,2,4-benzothiadiazine  
 1,1-dioxide;  
 3-ethyl-7-chloro-2H-1,2,4-benzothiadiazine  
 1,1-dioxide;

3-methyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-ethyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
5 3-n-pentyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-cyclopentyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-n-butyl-7-chloro-2H-1,2,4-benzothiadiazine  
10 1,1-dioxide;  
3-methyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-methyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
15 3,6-dimethyl-7-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3,7-dimethyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-(2,4,4-trimethylpentyl)-6-chloro-2H-1,2,4-  
20 benzothiadiazine 1,1-dioxide;  
3-octyl-6-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-dimethylaminoethoxymethyl-6-chloro-2H-1,2,4-  
benzothiadiazine 1,1-dioxide;  
25 3-cyclohexenyl-6-chloro-3,4-dihydro-2H-1,2,4-  
benzothiadiazine 1,1-dioxide;  
3-heptyl-8-chloro-2H-1,2,4-benzothiadiazine  
1,1-dioxide;  
3-styryl-8-chloro-3,4 dihydro-2H-1,2,4-  
30 benzothiadiazine 1,1-dioxide;  
3-propyl-6-methyl-2H-1,2,4-benzothiadiazine  
1,1-dioxide; and  
3-methoxy-6-ethyl-2H-1,2,4-benzothiadiazine  
1,1-dioxide.  
35 Such compounds and their preparation are described,  
for example, in U.S. Patents 2,986,572 and 4,184,039 which  
are hereby incorporated herein by reference.

Other stable free radical forming compounds

contemplated as being useful as hair growth stimulants in the present invention include spin labels and spin traps. Exemplary of these are: melanin; 4,4-dimethyl-3-oxazolinylloxy (hereinafter "doxyl") and derivatives such as 3-doxyl-5 $\alpha$ -cholestane, 3-doxyl-17 $\beta$ -hydroxy-5 $\alpha$ -androstane, 5-doxylstearic acid, 7-doxylstearic acid, 12-doxylstearic acid, 16-doxylstearic acid, 5-doxylstearic acid methyl ester, 7-doxylstearic acid methyl ester, 12-doxylstearic acid methyl ester, 16-doxylstearic acid methyl ester and the like; 2,2,5,5-tetramethyl-1-pyrrolidinyloxy (hereinafter "proxyl") and derivatives such as 3-(aminomethyl)-proxyl, 3-(2-[2-bromoacetamido]-acetamido)-proxyl, 3-(2-[2-bromoacetamido]-ethoxyethyl)-carbamoyl)-proxyl, 3-(2-bromoacetamido)-methyl)-proxyl, 3-(3-[2-bromoacetamido]-propylcarbamoyl)-proxyl, 3-(2-bromoacetamido)-proxyl, 3-carbamoyl-proxyl, 3-carboxy-proxyl, 3-cyano-proxyl, 3-(5-[dimethylamino]-1-naphthalene-sulfonamido)-proxyl, 3-(5-fluoro-2,4-dinitroanilino)-proxyl, 3-(2-[2-iodoacetamido]-acetamido)-proxyl, 3-(2-[2-iodoacetamido]-ethoxyethyl)-carbamoyl)-proxyl, 3-(2-iodoacetamidomethyl)-proxyl, 3-(3-[2-iodoacetamido]-propylcarbamoyl)-proxyl, 3-(2-iodoacetamido)-proxyl, 3-(2-[2-isothiocyanatoethoxy]-ethylcarbamoyl)-proxyl, 3-(2-isothiocyanatoethylcarbamoyl)-proxyl, 3-(isothiocyanatomethyl)-proxyl, 3-(3-isothiocyanato-propyl carbamoyl)-proxyl, 3-(2-[2-maleimidooethoxy]-ethylcarbamoyl)-proxyl, 3-(2-maleimidooethyl-carbamoyl)-proxyl, 3-(maleimidomethyl)-proxyl, 3-(3-maleimidopropyl-carbamoyl)-proxyl, 3-maleimidoproxyl, 3-(4-nitrophenoxy carbonyl)-proxyl, and the like; 2,2,6,6,-tetramethyl-1-piperidinyloxy (hereinafter "tempo") and derivatives such as 4-amino-tempo, 4-(2-bromoacetamido)-tempo, 4-(ethoxyfluorophosphinyloxy)-tempo, 4-hydroxy-tempo, 4-(2-iodoacetamido)-tempo, 4-isothiocyanato-tempo,

4-maleimido-tempo, 4-(4-nitrobenzoyloxy)-tempo,  
4-oxo-tempo, 4-phosphonooxy-tempo, and the like; other  
spin labels such as 2-(acetoxymercuri)-4,4,5,5-  
tetramethyl-2-imidazolin-1-yloxy-3-oxide, 3-carbamoyl-  
5 2,5-dihydro-2,2,5,5-tetramethyl-1H-pyrrol-1-yloxy,  
3,([ethoxycarbonyl]-oxycarbonyl)-2,5-dihydro-2,2,5,5-  
tetramethyl-1H-pyrrol-1-yloxy and the like; and nitrone  
and nitroso spin traps such as N-t-butyl- $\alpha$ -phenyl-nitrona,  
3,5-dibromo-4-nitroso-benzenesulfonic acid; 5,5-dimethyl  
10 -1-pyrroline N-oxide, 2-methyl-2-nitroso-propane,  
nitrosobenzene, nitrosodisulfonic acid,  $\alpha$ -(4-pyridyl-1-  
~~oxide)-N-t-butylnitrona,~~ 3,3,5,5-tetramethyl-pyrroline  
N-oxide, 2,4,6-tri-t-butylnitrosobenzene, and the like.  
Such spin labels and spin traps are commercially  
15 available.

Effective amounts of the hair growth stimulant  
generally range from about 0.01 to about 20 percent by  
weight of the composition, more preferably from about 0.1  
to about 10 percent by weight, most preferably from about  
20 0.5 to about 3 percent by weight, and especially about 2  
percent by weight, but more or less may be present in the  
composition depending on the particular hair growth  
stimulant. For convenience, reference is made hereinbelow  
25 to diphenyl hydantoin, but it is to be understood that the  
suitable substitutes therefor described above may be  
present partially or entirely in lieu of diphenyl  
hydantoin itself.

The second essential ingredient is an antiandrogen,  
preferably one which interferes with the binding of  
30 androgens such as dihydrotestosterone to receptors in hair  
follicles. However, antiandrogens which interfere with or  
inhibit the synthesis of androgenic compounds are also  
contemplated. The preferred compounds function primarily  
to block dihydrotestosterone receptors rather than to  
35 inhibit the reduction of testosterone, and are also known  
as DHT blockers. Exemplary of such antiandrogens are  
spironolactone, cyproterone, cyproterone acetate, and the

-10-

like. Of these, spironolactone is preferred because its effects from topical application are generally more limited to the local site of application.

Effective amounts of the antiandrogen generally range 5 from about 0.01 to about 5 percent by weight of the composition, but more or less than this may be used depending on the particular antiandrogen. The optimum amount is about one percent by weight of the composition for spironolactone and about 0.1 percent for cyproterone 10 and cyproterone acetate. Quite surprisingly, at amounts above these optimums, the effect of the antiandrogens is not as great, and for unknown reasons, in some cases the presence of the antiandrogen in the composition in amounts in substantial excess of the optimum may result in a 15 reduced effectiveness in stimulating hair growth in comparison to the composition containing no antiandrogen.

The hair growth stimulation effected by the present composition is improved when a free radical scavenger, preferably a hydroxyl radical scavenger, is present. As 20 used herein, the term "free radical scavenger" includes compounds which suppress free radical generation as well as compounds which react with free radicals in biological systems. Hydroxyl radical scavengers are, for example, sulfoxides, phosphine oxides, retinoids, purines, 25 pyrimidines, thiols, halide ions, aromatic hydrocarbons and the like. Free radical scavengers preferred in the composition of the present invention include those pharmaceutically acceptable hydroxyl radical scavengers which have a substantial effectiveness as a hydroxyl 30 radical scavenger, and especially compounds having an effectiveness as a hydroxyl radical scavenger substantially equivalent to or better than DMSO.

A preferred class of free radical scavengers includes sulfoxides of the formula  $R^8R^9SO$  wherein  $R^8$  is alkyl, 35 alkenyl, heteroalkyl (e.g. thiaalkyl or azaalkyl), hydroxyalkyl, or alkoxyalkyl having up to about 14 carbon atoms, and  $R^9$  is independently alkyl or hydroxyalkyl

having from 1 to about 8 carbon atoms. Examples of R<sup>8</sup> suitable herein include octyl, nonyl, decyl, undecyl, dodecyl, 3-decenyl, 2-dodecenyl, 3-undecenyl, 3-octenyl, 2-ketooctyl, 2-ketododecyl, 2-ketoundecyl, 2-ketododecyl, 5 2-hydroxyoctyl, 2-hydroxydecyl, 2-hydroxyundecyl, 2-hydroxydodecyl, 3-hydroxyundecyl, 3-methoxyundecyl, 2-methoxydodecyl, 3,6-dioxadodecyl, 2-ethylhexyl, and branched chain nonyl and dodecyl resulting from polymerization of three and four moles of propylene, 10 respectively. Examples of R<sup>9</sup> include methyl, ethyl, propyl, butyl, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, and 4-hydroxybutyl.

Especially preferred sulfoxides for the purposes of this invention are the dialkyl sulfoxides where R<sup>8</sup> is a hydrocarbyl alkyl or hydroxy-substituted alkyl group containing from 8 to 12 carbon atoms and R<sup>9</sup> is methyl, ethyl or propyl. As examples of these preferred sulfoxides there may be mentioned octyl methyl sulfoxide, nonyl methyl sulfoxide, decyl methyl sulfoxide, undecyl 15 methyl sulfoxide, dodecyl methyl sulfoxide, 2-hydroxydecyl methyl sulfoxide, 2-hydroxyundecyl methyl sulfoxide and 2-hydroxydodecyl methyl sulfoxide.

Another preferred class of hydroxyl radical scavengers includes the tertiary phosphine oxides of the formula R<sup>10</sup>R<sup>11</sup>R<sup>12</sup>P=O wherein R<sup>10</sup> is alkyl, aralkyl, heteroalkyl (e.g. azaalkyl or thiaalkyl), hydroxyalkyl, alkoxyalkyl, or ketoalkyl of from 1 to 14 carbon atoms, or aryl of from 6 to 12 carbon atoms, and R<sup>11</sup> and R<sup>12</sup> are independently alkyl, hydroxyalkyl, alkoxyalkyl or 20 ketoalkyl of from 1 to 4 carbon atoms. Examples of R<sup>10</sup> include methyl, ethyl, propyl, butyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, 2-propenyl, 3-decenyl, 2-dodecenyl, 3-undecenyl, 3-octenyl, 2-ketobutyl, 2-ketohexyl, 2-ketoocetyl, 2-ketododecyl, 30 2-ketoundecyl, 2-ketododecyl, 2-hydroxypropyl, 2-hydroxyhexyl, 3-hydroxyheptyl, 2-hydroxyoctyl, 2-hydroxyundecyl, 2-hydroxydodecyl, 3-hydroxyundecyl,

-12-

2-methoxybutyl, 3-methoxyundecyl, 2-methoxydodecyl,  
2-chlorodecyl, 3-chlorobutyl, 2-thiomethylhexyl,  
3,6-dioxadodecyl, 2-oxaheptyl, 3-azahexyl, 2-thiadecyl,  
2-ethylhexyl, phenyl, naphthyl, m-tolyl, benzyl, and  
5 branched chain nonyl and dodecyl resulting from  
polymerization of three and four moles of propylene,  
respectively.

Examples of R<sup>11</sup> and R<sup>12</sup> include methyl, ethyl,  
propyl, hydroxymethyl, 1-hydroxypropyl, 2-hydroxyethyl,  
10 and the like.

Especially preferred phosphine oxides for the purpose  
of this invention are those in which R<sup>10</sup> is a hydrocarbyl  
alkyl or hydroxy-substituted alkyl substituent containing  
from 8 to 12 carbon atoms and R<sup>11</sup> and R<sup>12</sup> are each methyl,  
15 ethyl or propyl. As examples of these preferred phosphine  
oxides there may be mentioned octyl dimethyl phosphine  
oxide, nonyl diethyl phosphine oxide, decyl dimethyl  
phosphine oxide, undecyl dimethyl phosphine oxide, dodecyl  
dimethyl phosphine oxide, 2-hydroxydecyl dimethyl phosphine  
20 oxide, 2-hydroxyundecyl dimethyl phosphine oxide and  
2-hydroxydodecyl dimethyl phosphine oxide. Dodecyl  
dimethyl phosphine oxide is especially preferred.

The retinoids comprise another preferred class of  
free radical scavengers. Exemplary retinoids include  
25 carotene, tretinoin, isotretinoin, 9-cis-tretinoin,  
retinol, retinol acetate, retinol palmitate,  
dehydroretinol, 9-cis-dehydroretinol,  
13-cis-dehydroretinol, 9,13-di-cis-dehydroretinol,  
retinal, etretinate, retinyl acetate,  
30 9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,  
8-nonatetraenoic acid and the like. Especially preferred  
retinoids include tretinoin and 9-(4-methoxy-2,3,6-  
trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid.

The free radical scavenger is preferably present in  
35 the composition in a proportion effective to,  
synergistically with the diphenyl hydantoin and  
antiandrogen, stimulate the growth of hair. The effective

amount depends on the particular free radical scavenger and its scavenging effectiveness, but is generally in the range of from 0.01 up to 50 percent by weight of the composition. For the sulfoxides such as DMSO, the effective amount is generally from about 5 to about 25 percent by weight of the composition, preferably about 15-20 percent by weight. Depending on the particular carrier, the amount of DMSO present may be adjusted to avoid phase separation. With free radical scavengers such as tretinoin, the effective amount is as little as 0.01-0.5 percent by weight. For convenience, reference is made hereinbelow to DMSO, but it is to be understood that other suitable free radical scavengers may be present, partially or entirely, in lieu of DMSO.

In some instances, the combined effect of the antiandrogen and free radical scavenger in the composition is sufficient to obtain acceptable hair growth stimulation without the presence of a hair growth stimulant per se. As examples of such compositions, there may be mentioned the combination of spironolactone with a sulfoxide such as DMSO or with a retinoid such as tretinoin. Such compositions, while generally less effective from the standpoint of the amount of hair growth and length of time to response, are generally nearly as effective as the composition with the hair growth stimulant from the standpoint of the proportion of those treated who eventually respond.

According to the method of the invention, the composition of the invention described above is applied topically to the skin to be treated, such as the scalp. Preferably, the application is once a day with a sufficient amount of the composition to cover the area at which the stimulation of hair growth is desired. It is contemplated that results are improved when the composition is applied after water-soaking the skin. Thus, a preferred embodiment of the method is convenient

-14-

in that the composition can be applied once daily immediately following bathing.

Generally, best results are obtained in treatment of bald or thinly-haired scalp areas in which hair loss has 5 not occurred for a period of time substantially in excess of about 3-5 years. The effectiveness also depends, although to a lesser degree, inversely on the age of the user.

10 The preparation and use of the composition is illustrated by way of the following examples.

Preparation of the Composition

Example 1

A composition according to the invention was prepared with the ingredients and proportions listed in Table I.

15

Table I

<u>Ingredient</u>	<u>Proportion</u>
Dermovan emulsion <sup>1</sup>	15 pounds
DMSO	3 pints
20 Water	2 pints
Propylene glycol	2 pints
Diphenyl hydantoin	0.5 wt.%
Spironolactone	0.5 wt.%

25

Notes for Table I:

1. Obtained from Owen Laboratories; Dermovan emulsion contains water, glycerol stearate, glycerin, mineral oil, synthetic spermaceti, cetyl alcohol, butylparaben, propylparaben and methylparaben.

30

The water and propylene glycol were added to the diphenyl hydantoin in a suitable container. The DMSO was then added and the mixture was thoroughly mixed and

-15-

allow d to stand overnight. Then, with constant stirring the Dermovan emulsion was added slowly. The mixture was then allowed to stand at least 24 hours with occasional stirring.

5

Example 2

A composition is prepared as in Example 1 except that 2.0 percent by weight of sodium diazoxide is substituted in place of the diazoxide and the proportion of spironolactone is decreased to 0.01 percent by weight.

10

Example 3

A topical gel was prepared with the following ingredients and proportions:

Table II

	<u>Ingredient</u>	<u>Proportion</u>
	DMSO	3 pints
	Propylene glycol	3 pints
	Water	3 pints
	Spironolactone	1 wt.%
20	Diphenyl hydantoin	1 wt.%
	Hydroxypropyl	1 wt.%
	cellulose (M.W. 100,000-1,000,000)	

25 The ingredients were combined with stirring and allowed to sit for 3-5 days until the mixture formed a gel.

Example 4

A lotion was prepared with the following ingredients and proportions:

-16-

Table III

<u>Ingredient</u>	<u>Proportion</u>
Propylene glycol	2 pints
5 Water	2 pints
Ethyl alcohol	6 pints
Urea	10 wt.%
Spironolactone	1 wt.%
Diphenyl hydantoin	1 wt.%
10	

The ingredients were combined with stirring to form a lotion.

#### Example 5

A cream was prepared as in Example 1, except that 1 pint of propylene glycol was used instead of 2 pints, 1 wt.% minoxidil was used instead of diphenyl hydantoin, 1 wt.% spironolactone instead of 0.5 wt.%, and also contained 0.01 wt.% tretinoïn added with the minoxidil and spironolactone.

#### Use of the Composition

#### Example 6

The composition of Example 1 was applied topically to the scalps of male patients with 2-5 years of hair loss who had all been previously treated with 2 wt.% minoxidil in a solution of water (70 vol.%), ethanol (15 vol.%) and propylene glycol (15 vol.%) without any significant promotion of hair growth. The composition of Example 1 was applied to the scalp twice daily at a rate of 1 ml/day. About half of the subjects responded with photographically verifiable hair growth after 2-6 months of treatment. In contrast, a control group similarly administered the composition of Example 1, but without any diphenyl hydantoin, exhibited less hair growth and had a

-17-

longer response time, although the number of subjects eventually responding was also about half of the group.

While I have described the composition and method of my invention above, many variations in the ingredients, 5 proportions, and manner of preparation will occur to those skilled in the art. It is intended that all such variations which fall within the scope and spirit of the appended claims be embraced thereby.

-18-

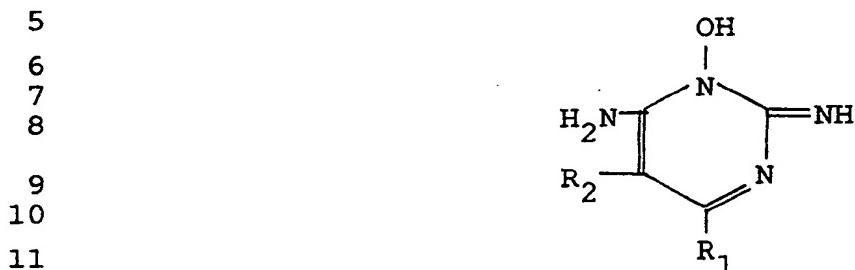
CLAIMS:

- 1        1. A composition for topical application to the  
2 skin to stimulate hair growth, comprising:
  - 3            (a) a hair growth stimulant;
  - 4            (b) an antiandrogen; and
  - 5            (c) a pharmaceutical carrier in which said hair  
6 growth stimulant and said antiandrogen are substantially  
7 homogenously dispersed.
- 1        2. The composition of claim 1, wherein said hair  
2 growth stimulant is a substance which forms a stable free  
3 radical.
- 1        3. The composition of claim 2, wherein said hair  
2 growth stimulant is selected from the group consisting of:  
3 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-  
4 2-iminopyridines, porphyrins, 1,2,4-benzothiadiazine  
5 1,1-dioxides, 5,5-diaryl hydantoins, and nitroxide,  
6 nitroso and nitrone spin labels and spin traps.
- 1        4. The composition of claim 1, wherein said  
2 antiandrogen interferes with the binding of  
3 dihydrotestosterone to receptors.
- 1        5. The composition of claim 2, further comprising a  
2 free radical scavenger.
- 1        6. The composition of claim 5, wherein said free  
2 radical scavenger is selected from the group consisting  
3 of: sulfoxides, tertiary phosphine oxides, and retinoids.
- 1        7. A composition for topical application to the  
2 skin to stimulate hair growth, comprising:
  - 3            (a) a pharmacologically acceptable substance  
4 which forms a stable free radical;

5                         (b) an antiandrogen; and  
 6                         (c) a pharmaceutical carrier in which said hair  
 7                         growth stimulant and said antiandrogen are substantially  
 8                         homogenously dispersed.

1                         8. The composition of claim 7, wherein said stable  
 2                         free radical forming substance is selected from the group  
 3                         consisting of: 6-amino-4-(substituted amino)-1,2-dihydro-  
 4                         1-hydroxy-2-iminopyrimidines, porphoryns, 5,5-diaryl  
 5                         hydantoins, 1,2,4-benzothiadiazine 1,1-dioxides,  
 6                         nitroxide, nitroso and nitrone spin labels and traps.

1                         9. The composition of claim 7, wherein said stable  
 2                         free radical forming substance is a 1,2-dihydro-1-  
 3                         hydroxypyrimidine compound selected from the group  
 4                         consisting of compounds of the formula:



12                         wherein R<sub>1</sub> is a moiety selected from the group consisting  
 13                         of moieties of the formula:



17                         wherein R<sub>3</sub> and R<sub>4</sub> are selected from the group consisting  
 18                         of hydrogen, lower alkyl, lower alkenyl, lower aralkyl,  
 19                         and lower cycloalkyl, and taken together, R<sub>3</sub> and R<sub>4</sub> may be  
 20                         a heterocyclic moiety selected from the group consisting  
 21                         of aziridinyl, azetidinyl, pyrrolidinyl, piperidino,  
 22                         hexahydroazepinyl, heptamethylenimino, octamethylenimino,  
 23                         morpholino and 4-lower-alkyl-piperazinyl, each of said

-20-

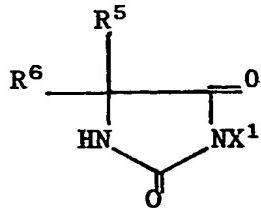
24 hetrocyclic moieties having attached as substituents on  
25 the carbon atoms thereof 0-3 lower alkyl groups, hydroxy  
26 or alkoxy, and wherein R<sub>2</sub> is selected from the group  
27 consisting of hydrogen, lower alkyl, lower alkenyl, lower  
28 alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl,  
29 lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl,  
30 and the tautomers and pharmacologically acceptable acid  
31 addition salts thereof.

1 10. The composition of claim 9, wherein said stable  
2 free radical forming substance is minoxidil.

1 11. The composition of claim 7, wherein said stable  
2 free radical forming substance is a porphyrin.

1 12. The composition of claim 11, wherein said  
2 porphyrin is selected from the group consisting of:  
3 uroporphyrin, coproporphyrin and protoporphyrin.

1 13. The composition of claim 7, wherein said stable  
2 free radical forming substance is selected from hydantoins  
3 of the formula:



9 wherein R<sup>5</sup> and R<sup>6</sup> are independently aryl, alkaryl,  
10 haloaryl, alkoxyaryl, heteroaryl, aminoaryl, or taken  
11 together, R<sup>5</sup> and R<sup>6</sup> are diarylene, and X<sup>2</sup> is hydrogen,  
12 alkali metal, alkaline earth metal, ammonium, alkylamine,  
13 alkanolamine or polymethylenediamine.

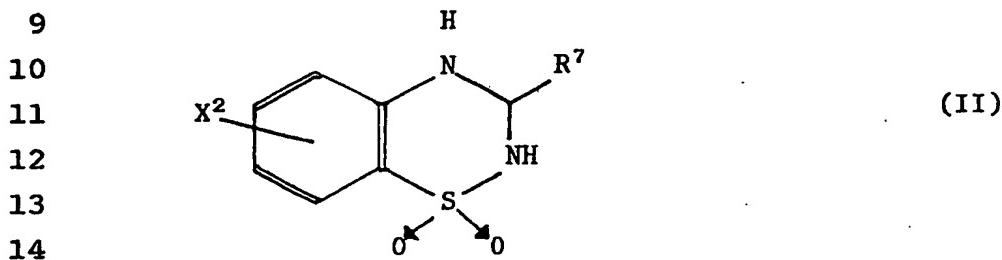
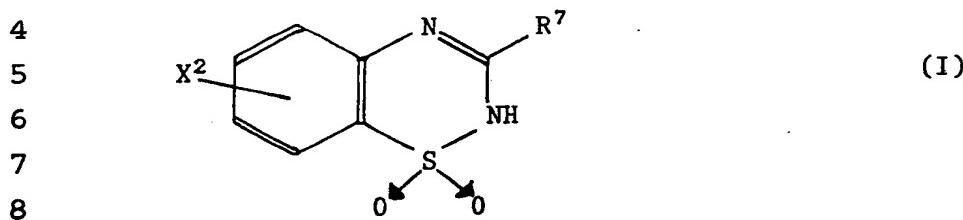
-21-

1        14. The composition of claim 13, wherein said  
 2        hydantoin is selected from the group consisting of:  
 3        5,5-diphenylhydantoin, 5-phenyl-5-(p-bromophenyl)-  
 4        hydantoin, 5-phenyl-5-(p-chlorophenyl)-hydantoin, 5,5-di-  
 5        (p-dimethylaminophenyl)-hydantoin, 5-diphenylene-  
 6        hydantoin, 5-xylenyl-5-phenylhydantoin, 5,5-(di-p-tolyl)-  
 7        hydantoin, 5-phenyl-5-anisylhydantoin, 5-phenyl-5-(2-  
 8        thienyl)-hydantoin, and salts thereof.

1        15. The composition of claim 7, wherein said stable  
 2        free radical forming substance is 5,5-diphenylhydantoin or  
 3        a salt thereof.

1        16. The composition of claim 7, wherein said stable  
 2        free radical forming substance is a 1,2,4-benzothiadiazine  
 3        1,1-dioxide.

1        17. The composition of claim 16, wherein said  
 2        1,2,4-benzothiadiazine 1,1-dioxide is selected from  
 3        compounds of the formulae:



15 wherein X<sup>2</sup> is chlorine, bromine or trifluoromethyl in the  
16 6, 7, 8 or 9 position or lower alkyl or lower alkoxy in  
17 the 6 position, and R<sup>7</sup> is alkyl, dialkylaminoalkoxyalkyl,  
18 or aralkyl, and pharmacologically acceptable acid addition  
19 salts thereof.

1        18. The composition of claim 17 wherein said  
2        1,2,4-benzothiadiazine 1,1-dioxide is selected from the  
3        group consisting of:

4                3-methyl-7-chloro-2H-1,2,4-benzothiadiazine 1,1-  
5        dioxide;  
6                3-ethyl-7-chloro-2H-1,2,4-benzothiadiazine 1,1-  
7        dioxide;  
8                3-methyl-6-chloro-2H-1,2,4-benzothiadiazine 1,1-  
9        dioxide;  
10              3-ethyl-6-chloro-2H-1,2,4-benzothiadiazine 1,1-  
11        dioxide;  
12              3-n-pentyl-6-chloro-2H-1,2,4-benzothiadiazine 1,1-  
13        dioxide;  
14              3-cyclopentyl-6-chloro-2H-1,2,4-benzothiadiazine  
15        1,1-dioxide;  
16              3-n-butyl-7-chloro-2H-1,2,4-benzothiadiazine 1,1-  
17        dioxide;  
18              3-methyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine  
19        1,1-dioxide;  
20              3-methyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine  
21        1,1-dioxide;  
22              3,6-dimethyl-7-chloro-2H-1,2,4-benzothiadiazine 1,1-  
23        dioxide;  
24              3,7-dimethyl-6-chloro-2H-1,2,4-benzothiadiazine 1,1-  
25        dioxide;  
26              3-(2,4,4-trimethylpentyl)-6-chloro-2H-1,2,4-  
27        benzothiadiazine 1,1-dioxide;  
28              3-octyl-6-chloro-2H-1,2,4-benzothiadiazine 1,1-  
29        dioxide;  
30              3-dimethylaminoethoxymethyl-6-chloro-2H-1,2,4-  
31        benzothiadiazine 1,1-dioxide;

32                   3-cyclohexenyl-6-chloro-3,4-dihydro-2H-1,2,4-  
33     benzothiadiazine 1,1-dioxide;  
34                   3-heptyl-8-chloro-2H-1,2,4-benzothiadiazine 1,1-  
35     dioxide;  
36                   3-styryl-8-chloro-3,4        dihydro-2H-1,2,4-  
37     benzothiadiazine 1,1-dioxide;  
38                   3-propyl-6-methyl-2H-1,2,4-benzothiadiazine 1,1-  
39     dioxide;  
40                   3-methoxy-6-ethyl-2H-1,2,4-benzothiadiazine 1,1-  
41     dioxide; and  
42                   pharmacologically acceptable acid addition salts  
43     thereof.

1                  19. The composition of claim 17, wherein said stable  
2     free radical forming substance is  
3     7-chloro-3-methyl-2H-1,2, 4-benzothiadiazine 1,1,-dioxide  
4     or a salt thereof.

1                  20. The composition of claim 7, wherein said stable  
2     free radical forming substance is selected from the group  
3     consisting of derivatives of 4,4-dimethyl-3-oxazolinylloxy,  
4     2,2,5,5-tetramethyl-1-pyrrolidonyloxy        and  
5     2,2,6,6-tetramethyl-1-piperidinyloxy.

1                  21. The composition of claim 20, wherein said stable  
2     free radical forming substance is selected from the group  
3     consisting of:        3-doxyl-5 $\alpha$ -cholestane,  
4     3-doxyl-17 $\beta$ -hydroxy-5 $\alpha$ -androstane, 5-doxylstearic acid,  
5     7-doxylstearic acid, 12-doxylstearic acid, 16-doxylstearic  
6     acid, 5-doxylstearic acid methyl ester, 7-doxylstearic  
7     acid methyl ester, 12-doxylstearic acid methyl ester and  
8     16-doxylstearic acid methyl ester.

1                  22. The composition of claim 20, wherein said stable  
2     free radical forming substance is selected from the group  
3     consisting of:    3-(aminomethyl)-proxyl,   3-(2-[2-  
4     bromoacetamido]-acetamido)-proxyl,

-24-

5      3-(2-[2-bromoacetamido)-ethoxyethyl]-carbamoyl)-proxyl,  
6      3-(2-bromoacetamido)-methyl)-proxyl,                3-(3-[2-  
7      bromoacetamido]-propylcarbamoyl)-proxyl,                3-(2-  
8      bromoacetamido)-proxyl, 3-carbamoyl-proxyl, 3-carboxy-  
9      proxyl, 3-cyano-proxyl, 3-(5-[dimethylamino]-1-  
10     naphthalene-sulfonamido)-proxyl,                3-(5-fluoro-2,4-  
11     dinitroanilino)-proxyl, 3-(2-[2-iodoacetamido]-acetamido)  
12     -proxyl, 3-(2-[2-iodoacetamido)-ethoxyethyl]-carbamoyl)  
13     -proxyl, 3-(2-iodoacetamidomethyl)-proxyl,        3-(3-[2-  
14     iodoacetamido]-propylcarbamoyl)-proxyl,        3-(2-  
15     iodoacetamido)-proxyl,        3-(2-[2-isothiocyanatoethoxy]-  
16     ethylcarbamoyl)-proxyl, 3-(2-isothiocyanatoethylcarbamoyl)-  
17     proxyl, 3-(isothiocyanatomethyl)-proxyl, 3-(3-isothiocyanato-  
18     propyl carbamoyl)-proxyl, 3-(2-[2-maleimidoethoxy]-  
19     ethylcarbamoyl)-proxyl, 3-(2-maleimidoethyl-carbamoyl)-  
20     proxyl, 3-(maleimidomethyl)-proxyl, 3-(3-maleimidopropyl-  
21     carbamoyl)-proxyl and 3-maleimidoproxyl, 3-(4-nitrophenoxy  
22     carbonyl)-proxyl.

1       23. The composition of claim 20, wherein said stable  
2       free radical forming substance is selected from the group  
3       consisting of: 4-amino-tempo, 4-(2-bromoacetamido)-tempo,  
4       4-(ethoxyfluorophosphinyloxy)-tempo, 4-hydroxy-tempo, 4-(2-  
5       iodoacetamido)-tempo, 4-isothiocyanato-tempo, 4-maleimido-  
6       tempo, 4-(4-nitrobenzoyloxy)-tempo, 4-oxo-tempo, and  
7       4-phosphonoxy-tempo.

1       24. The composition of claim 7, wherein said stable  
2       free radical forming substance is selected from the group  
3       consisting of: 2-(acetoxymercuri)-4,4,5,5-tetramethyl-2-  
4       imidazolin-1-yloxy-3-oxide, 3-carbamoyl-2,5-dihydro-2,2,5,  
5       5-tetramethyl-1H-pyrrol-1-yloxy, and 3,([ethoxycarbonyl]-  
6       oxycarbonyl)-2,5-dihydro-2,2,5,5-tetramethyl-1H-pyrrol-  
7       1-yloxy.

1        25. The composition of claim 7, wherein said stable  
2 free radical forming substance is selected from the group  
3 consisting of: N-t-butyl- $\alpha$ -phenyl-nitrone, 3,5-dibromo-  
4 4-nitroso-benzenesulfonic acid; 5,5-dimethyl-1-pyrroline  
5 N-oxide, 2-methyl-2-nitroso-propane, nitrosobenzene,  
6 nitrosodisulfonic acid,  $\alpha$ -(4-pyridyl-1-oxide)-N-t-  
7 butylnitrone, 3,3,5,5-tetramethyl-pyrroline N-oxide, and  
8 2,4,6-tri-t-butylnitrosobenzene.

1        26. The composition of claim 7, wherein said  
2 antiandrogen interferes with the binding of  
3 dihydrotestosterone to receptors.

1        27. The composition of claim 7, wherein said  
2 antiandrogen is selected from the group consisting of:  
3 spironolactone, cyproterone, cyproterone acetate, and  
4 combinations thereof.

1        28. The composition of claim 7, wherein said carrier  
2 is an occlusive or semiocclusive carrier selected from the  
3 group consisting of water-in-oil emulsions and oil-in-water  
4 emulsions.

1        29. The composition of claim 7, further comprising a  
2 free radical scavenger homogenously dispersed in said  
3 carrier in an amount less than 50 percent by weight of the  
4 composition.

1        30. The composition of claim 29, wherein said free  
2 radical scavenger is selected from the group consisting of  
3 sulfoxides, tertiary phosphine oxides and retinoids.

1        31. The composition of claim 29, wherein said free  
2 radical scavenger is a sulfoxide of the formula  $R^8R^9SO$   
3 wherein  $R^8$  is alkyl, alkenyl, heteroalkyl, hydroxyalkyl or  
4 alkoxyalkyl having up to about 14 carbon atoms, and  $R^9$

5      is independently alkyl or hydroxyalkyl having from 1 to 8  
6      carbon atoms.

1            32. The composition of claim 31, wherein R<sup>8</sup> is alkyl  
2      or β-hydroxyalkyl having up to 14 carbon atoms and R<sup>9</sup> is  
3      methyl.

1            33. The composition of claim 32, wherein R<sup>8</sup> is  
2      methyl.

1            34. The composition of claim 30, wherein said free  
2      radical scavenger is a tertiary phosphine oxide of the  
3      formula R<sup>10</sup>R<sup>11</sup>R<sup>12</sup>PO wherein R<sup>10</sup> is alkyl, aryl, aralkyl,  
4      heteroalkyl, hydroxyalkyl, alkoxyalkyl, or ketoalkyl  
5      having up to 14 carbon atoms and R<sup>11</sup> and R<sup>12</sup> are  
6      independently alkyl, hydroxyalkyl, alkoxyalkyl or  
7      ketoalkyl having up to 4 carbon atoms.

1            35. The composition of claim 29, wherein said free  
2      radical scavenger is an alcohol selected from the group  
3      consisting of methanol, ethanol, propanol, butanol,  
4      ethylene glycol, and propylene glycol.

1            36. The composition of claim 7, further comprising a  
2      retinoid.

1            37. The composition of claim 36, wherein said  
2      retinoid is selected from the group consisting of:  
3      carotene, tretinoin, isotretinoin, 9-cis-tretinoin,  
4      retinol, retinol acetate, retinol palmitate,  
5      dehydroretinol, 9-cis-dehydroretinol, 13-cis-  
6      dehydroretinol, 9,13-di-cis-dehydroretinol, retinal,  
7      etretinate, retinyl acetate, and 9-(4-methoxy-2,3,6-  
8      trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic  
9      acid.

-27-

1           38. The composition of claim 36, wherein said  
2       retinoid is tretinoïn or 9-(4-methoxy-2,3,6-  
3       trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid.

1           39. A topical hair growth stimulating composition,  
2       comprising:

3                 from about 0.5 to about 3 percent by weight  
4       5,5,-diphenyl hydantoin;

5                 from about 0.01 to about 5 percent by weight  
6       spironolactone; and

7                 from about 5 to about 25 percent by weight  
8       dimethyl sulfoxide;

9                 substantially homogenously dispersed in a  
10      pharmaceutical carrier.

1           40. A topical hair growth stimulating composition,  
2       comprising:

3                 from about 0.5 to about 3 percent by weight  
4       5,5,-diphenyl hydantoin;

5                 from about 0.01 to about 5 percent by weight  
6       spironolactone; and

7                 from about 0.01 to about 0.5 percent by weight  
8       tretinoïn;

9                 substantially homogenously dispersed in a  
10      pharmaceutical carrier.

1           41. A topical hair growth stimulating composition,  
2       comprising:

3                 from about 0.01 to about 5 percent by weight  
4       spironolactone; and

5                 from about 5 to about 25 percent by weight  
6       dimethyl sulfoxide;

7                 substantially homogenously dispersed in a  
8       pharmaceutical carrier.

-28-

1       42. A topical hair growth stimulating composition,  
2 comprising:  
3              from about 0.01 to about 5 percent by weight  
4       spironolactone; and  
5              from about 0.01 to about 0.5 percent by weight  
6       tretinoin;

7              substantially homogenously dispersed in a  
8 pharmaceutical carrier.

1       43. A topical hair growth stimulating composition,  
2 comprising:  
3              from about 0.5 to about 3 percent by weight  
4       diazoxide;  
5              from about 0.01 to about 5 percent by weight  
6       spironolactone; and  
7              from about 5 to about 25 percent by weight  
8       dimethyl sulfoxide;

9              substantially homogenously dispersed in a  
10 pharmaceutical carrier.

1       44. A topical hair growth stimulating composition,  
2 comprising:  
3              from about 0.5 to about 3 percent by weight  
4       diazoxide;  
5              from about 0.01 to about 5 percent by weight  
6       spironolactone; and  
7              from about 0.01 to about 0.5 percent by weight  
8       tretinoin;

9              substantially homogenously dispersed in a  
10 pharmaceutical carrier.

1       45. A topical hair growth stimulating composition,  
2 comprising:  
3              from about 0.5 to about 3 percent by weight  
4       minoxidil;

5              from about 0.01 to about 5 percent by weight  
6       spironolactone; and

-29-

7               from about 5 to about 25 percent by weight  
8 dimethyl sulfoxide;  
9                substantially homogenously dispersed in a  
10 pharmaceutical carrier.

1               46. A topical hair growth stimulating composition,  
2 comprising:  
3                from about 0.5 to about 3 percent by weight  
4 minoxidil;  
5                from about 0.01 to about 5 percent by weight  
6 spironolactone; and  
7                from about 0.01 to about 0.5 percent by weight  
8 tretinoin;  
9                substantially homogenously dispersed in a  
10 pharmaceutical carrier.

# INTERNATIONAL SEARCH REPORT

International Application No PCT/US88/00232

## I. CLASSIFICATION & SUBJECT MATTER (if several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61K 7/06, A61K 31/625, A61K 31/425, A61K 31 /495

U.S.Cl.: 424/70, 514/175, 514/237, 514/275

## II. FIELDS SEARCHED

Minimum Documentation Searched ?

Classification System	Classification Symbols
U.S.	424/70, 514/175, 514/237, 514/275

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT \*

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
X	U.S., A, 3,551,554, (HERSCHLER), 29 December 1970, Col. 11, lines 1 to 35, col. 12, lines 50 to 75 and col. 17, lines 50 to 67.	1 to 46
X	U.S., A, 4,139,619, (CHIDSEY) 13 February 1979, col. 2, lines 20 to 50.	1 to 46
X	N, Chemical Abstracts, issued May 7, 1973, (Columbus, Ohio, U.S.A.), Vol. 78, page 2, column 2, Abstract No. 115239n Robert Herschler, Compositions for Topical Application for Enhancing Tissue Penetration of Physiologically Active Agents with Dimethyl Sulfoxide.	1 to 46
X	N, FDA Consumer, issued February 10, 1981, page 10, col. 2, lines 37 to 44 (Rockville, Maryland, U.S.A.), Richard C. Thompson, Balding is Forever, Experts Say.	1 to 46

\* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed Invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed Invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search

02 MAY 1988

International Searching Authority

ISA/US

Date of Mailing of this International Search Report

16 MAY 1988

Signature of Authorized Officer

Dale R. O're